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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,762	12/27/2005	Massimo Ferrari	207,385	8763

7590 03/01/2010

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EXAMINER	
MABRY, JOHN	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
03/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,762	FERRARI ET AL.	
	Examiner	Art Unit	
	JOHN MABRY	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 10, 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-43 and 47-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-43 and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/10/09 has been entered.

Response to Applicant's Remarks

Applicant's response on December 10, 2009 filed in response to the Office Action dated July 20, 2009 has been received and duly noted.

In view of this response, the status of the rejections/objections of record is as follows:

Status of the Claims

Claims 26-43 and 47-49 are pending and rejected.

Claims 1-25 and 44-46 have been cancelled.

Claim Rejections - 35 USC § 103

Claims 26-46 and 47-49 rejections are withdrawn under 35 U.S.C. 103(a) as being unpatentable under 35 U.S.C. 103(a) as being unpatentable over Alt (US 5,512,684).

A new rejection under 35 U.S.C. 103(a) as being unpatentable under 35 U.S.C. 103(a) as being unpatentable over Alt (US 5,512,684) in view of Gandolfi et al (US 4,999,362) and in view of Dorwald (Side Reactions in Organic Synthesis 2005, Wiley-VCH, page 2)is shown below:

The instant application claims a process for the preparation of raloxifene hydrochloride (I) by reaction of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (II) to make 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene (III) then protecting with an acetylating agent, particularly acetic anhydride in presence of triethyl amine, to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV). The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) without isolating the product. The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene is deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride, I).

Scope & Content of Prior Art MPEP 2141.01

Alt describes a process as illustrated in Scheme III (columns 5/6) for the preparation of raloxifene hydrochloride (I) by reaction of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (II) (R=C1-C6 alkyl, column 2, lines 8-9 and see "Dealkylation" in column 7) to make 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene (III) then protecting with an acetylating agent, particularly acetic anhydride in presence of triethyl amine, to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) (see "Reprotection" in bottom of column 7 column 8, lines 1-5). The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) then isolating the crude product (see "Acylation" in column 9, lines 22-23, lines 37-41). The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) is deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene – the desired product (see "Deprotection of Reprotected Dihydroxythiophenes" in bottom of column 10 - column 11, lines 63-67 and lines 1-22).

Experimentally, the deprotection of 6-acetoxy compound is converted to the deprotected 6-hydroxy compound by addition of sodium hydroxide in methanol. The

solvent was then removed, extracted with organic solvent, acidified to pH 2-3 then made basic and continually worked up to yield a solid under vacuum. The crude product was purified by crystallization and column chromatography to yield the desired product in pure form (see column 15, lines 29-67 and column 16, lines 1-48).

Differences between Prior Art & the Claims MPEP 2141.02

Alt differs from the instant application in the following ways.

(a) Alt isolates the crude product, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) prior to converting to desired product (I) versus Applicant's did not isolate 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI).

(b) The instant application describes a crystallization of the final product compared to Alt's acid-base work up and chromatography purification and

(c) The instant applicant claims a process for the HCl salt of compound I compared to the seemingly neutral form (free amine) of Alt's.

Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413

It would be obvious to one of ordinary skill in the art at the time when the invention was made to initiate the synthesis of the desired final product, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride) by the process as described by Alt.

(a) Alt differs from the instant application in the following ways. Alt isolates the crude product, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) prior to converting to desired product (I) versus Applicant's did not isolate 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI).

Applicant argues that Examiner does not provide any motivation as to why one of ordinary skill in the art avoid the step of isolating 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) and proceeding to the final product (I) *in situ* by addition of a strong acid, in particularly hydrochloric acid.

It is well within the purview of the skilled artisan in the relevant art to reduce steps in order to achieve the desired product faster and in higher yields.

Dorwald clearly states that in the design of an organic molecule, a synthetic chemist would need to analyze *"the shortest synthetic strategies which are most likely to give rapid access to the target compound, ideally in high yield and purity"* – see page 2 under 1.2 Synthesis Design.

Again, an artisan of ordinary skill, in this case, an organic chemist, would be motivated to take the prior art of Alt '684 and reduce the step of isolation of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) in order to achieve the final product (I) in greater yield and higher purity.

(b) It would be obvious to an artisan of ordinary skill in the art at the time the invention was made to convert the free-form (neutral) compounds of formula (I) and

convert said compounds into the corresponding salts for the purposes of obtaining higher purity (decreased side reactions), higher yields and prevention of compound instability. In similar structural compounds, Gandolfi discloses the advantages of obtaining the salts of neutral compounds: increased stability, increased solubility, decreased solubility and ease of crystallization (see column 4, lines 60-63) which contributes to higher purity (decreased side reactions) and higher yields. These salts can be selected from: hydrochlorides and other commonly known and art accepted acids (see column 4, lines 54-59). An artisan of ordinary skill in the art would be highly motivated to combine the compounds of Alt along with the teachings of Gandolfi in order to produce salt compounds of formula I that would lead to higher purity (decreased side reactions), prevention of compound instability and higher yields in the process of synthesizing raloxifene hydrochloride.

Furthermore, Alt suggests that HCl salt formation of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene is conveniently formed by reacting the compound with hydrochloric acid which are quickly formed in high yields. These salts are formed by isolating the compound from a suitable acid wash as the final step of the synthesis. The preferred salt is the hydrochloric salt (see column 12, lines 35-67 and column 13, lines 1-6).

The adjustment of particular conventional working conditions (e.g. determining result effective amounts of the ingredients beneficially taught by the cited references), as well as adjustment of reaction temperature, reaction time and use of solvents,

interchanging a particular acid and/or base, not isolating intermediates, is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan (*In re* Mostovych, Weber, Mitchell and Aulbach, 144 USPQ 38). Accordingly, these types of modifications would have been well within the purview of the skilled artisan and no more than an effort to optimize results.

The procedure, steps of synthesis and reactions conditions are all described that would motivate one of ordinary skill in the art to make minor and obvious experimental adjustments in order to achieve high yields and high purity of desire product, (I).

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor,

Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/
Examiner
Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625